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23914 7590 01/29/2009 LOUIS J. WILLE BRISTOL-MYERS SQUIBB COMPANY PATENT DEPARTMENT P O BOX 4000 PRINCETON, NJ 08543-4000				
EXAMINER GAMBEL, PHILLIP				
ART UNIT		PAPER NUMBER		
1644				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/057,288

Applicant(s)

LARSEN ET AL.

Examiner

Phillip Gambel

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 October 2008.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5,6,9,10,12,13,30,33,34,36,37,44-52,54-60 and 62-77 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1,2,5,6,9,10,12,13,30,33,34,36,37,44-52,54-60 and 62-77 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-848)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 05/09/2008
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

1. Applicant's amendment, filed 10/21/2008, has been entered.

Claims 1, 6, 9, 13, 34, 37, 46, 55, 56, 62, 64, 67-70 and 73 have been amended.

Claims 75-77 have been added.

Claims 1-2, 5-6, 9-10, 12-13, 30, 33-34, 36-37, 44-52, 54-60 and 62-77 are pending.

Claims 3-4, 7-8, 11, 14-17, 18-29, 31-32, 35, 38-43, 53 and 61 have been canceled previously.

2. The following of record is reiterated for clarity and convenience.

As indicated previously, applicant's election of the following species:

the alkylating agent is busulfan;
the first ligand is a soluble CTLA4;
the second ligand is anti-CD40 antibody; and
the targeted condition is solid organ or tissue/cellular transplant
with traverse has been acknowledged.

As indicated previously, given amending the claims to provide the alkylating agent / busulfan after the administration of bone marrow derived stem cells,

the search has been extended to another alkylating agent (i.e. cyclophosphamide) in view of the enablement issues under 35 USC 112, first paragraph, indicated herein for "administering the elected alkylating agent busulfan after the administration of bone marrow cells / stem cells" indicated below and in the interest of compact prosecution.

Claims 1-6, 9-13, 17, 28-37 and 44-52 and 54-60 and 62-74 are being examined to the extent that they read on the elected species (e.g. busulfan as well as cyclophosphamide, the first ligand is a soluble CTLA4, the second ligand is anti-CD40 antibody and the targeted condition is solid organ or tissue/cellular transplant) for examination purposes in the instant application.

Applicant's amendment, filed 12/18/06, acknowledged the species election.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Office Action will be in response to applicant's arguments, filed 10/21/2008.

The rejections of record can be found in the previous Office Actions.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

See the previous Office Actions for a more complete analysis of the rejections of record.

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4. Priority.

The filing date of the instant claims is deemed to be the filing date of priority application USSN 60/303,142, filed 07/05/2001.

Applicant's assertions, filed 10/21/2008, concerning the priority of the instant claims have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal concerning the priority of the instant claims are essentially the same of record and reiterated herein for applicant's convenience.

In contrast to applicant's continual reliance and assertions of inferring "limitations", the disclosure of experimental observations concerning the ability of a single dose of busulfan prior to the transplantation (i.e. intravenous infusion) of T cell-depleted bone marrow cells (e.g. comprising hemopoietic stem cells) in priority USSN 60/264,528, filed 1/26/05;

does not provide sufficient written description for

- (a) "administering TDBM before, during and/or after a solid organ or tissue/cellular transplant";
- (b) "subsequently administering an alkylating agent wherein the alkylating agent is selected from a group consisting of alkylsulfonates, nitrogen mustards, oxazapospirines, nitrosoureas, (including busulfan)"; or
- (c) "administering an costimulatory blockade before, during and/or after a solid organ or tissue/cellular transplant blockade which costimulatory blockade comprises a combination of a first ligand that interferes with binding of CD28 to either CD80 or CD86, and a second ligand that interferes with binding of CD154 to CD40"; as currently claimed.

Further, the priority application USSN 60/264,528, filed 1/26/01 does not appear to provide sufficient written support for

- all of the claimed dosage amounts and administration timing (e.g., see claims 30, 57-60, 62-63);
 - all of the claimed characteristics of the claimed soluble CTLA4 molecule (e.g., see claims 44-50, 65-, 73-74);
 - all of the claimed alkylating agents (e.g., see claims 63-64) nor
 - all of the claimed ligands for CD40 (e.g., see claims 52 and 54-55)
- currently recited in the instant application.

These instant claims encompass limitations that represent a departure from the priority USSN 60/264,528, filed 1/26/05.

For example, applicant's continual reliance on a limited disclosure and possibly a single or limited species (e.g. busulfan) under certain defined conditions do/does not provide sufficient direction and guidance to the written description of the currently claimed "limitations" "wherein the alkylating agent is selected from a group consisting of alkylsulfonates, nitrogen mustards, oxazapospirines, nitrosoureas" as well as all of the currently claimed dosage amounts and administration timing.

Further, priority application USSN 60/264,528, filed 1/26/01, provides for CTLA4-Ig (versus generic "first ligand that interferes with binding of CD28 to either CD40 or CD86 or the currently claimed CTLA4 modified / mutant molecules) and the anti-CD40L monoclonal antibody only (versus generic "second ligand that interferes with binding of CD154 to CD40).

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Therefore, as indicated previously, priority application USSN 60/264,528, filed 1/26/01 does not appear to support the instant claims encompassing methods of inhibiting rejection of a solid organ or tissue/cellular transplant by administering an alkylating agent wherein the alkylating agent is selected from a group consisting of alkylsulfonates, nitrogen mustards, oxazapospirines, nitrosoureas (versus experimental conditions using busulfan only) and subsequently administering cell depleted bone marrow cells before, during or after as the transplant, as well as administering CD28 / CD80 / CD86 / CD154 / CD40 inhibitors.

It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Therefore, the filing date of the instant claims is still deemed to be the filing date of priority application USSN 60/303,142, filed 07/05/2001.

If applicant desires priority prior to 07/05/2001; applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earliest priority application asserted.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Applicant's arguments filed 10/21/2008 in the appeal Brief have been fully considered but have not been found convincing essentially for the reasons of record.

Once again, applicant relies upon specific conditions of Examples / Experimental Observations as addressed previously and reiterated above to support broader claims and limitations currently claimed.

Again, applicant's arguments (e.g., see pages 82-22 of applicant's Remarks, filed 10/21/2008) are based

- upon a skin graft experiment of administering TDBM on the same day and day six (b) after transplant and re-challenging with skin transplant" to support "before, during and/or after a solid organ or tissue/cellular transplant" broadly recited currently (in addition to specific experimental times, the ordinary artisan would not appreciate that re-challenging in an experimental skin graft model as testing the survival of skin grafts and the nature of the immunological non-responsiveness as an example of prior administration in a therapeutic setting);

- upon one experiment of administration on specific days (day 0, day 5 and day 6) of administering busulfan as support for the subsequently administering an alkylating agent" broadly recited currently (note that the recitation of "subsequently" is broader than day 5 and day 6 and that alkylating agent is broader than busulfan described in the one experiment relied upon by applicant)"

- upon administration on specific days (days 0, 2, 4, 6, 14, 28) of administering of specific inhibitors of costimulatory molecules as support for the broader limitations of "before, during and/or after", as currently recited;

- upon the species of "busulfan" for the broader limitation encompassing "alkylating agents", as currently recited;

- upon the reliance that a physician would understand the appropriate dosages in view of applicant's disclosure and the history of individual subjects to the "dosage amounts and administration timing", as currently claimed; and

upon the disclosure of the species of CTLA4Ig and anti-CD40L antibody to the broader soluble CTLA4 molecule and CD40 ligands, as currently claimed.

Again, as addressed previously and reiterated above, the entitlement to a filing date does not extend to subject matter that is not disclosed but would be obvious over with is expressly discloses. Priority only extends only to that which is disclosed.

5. Enablement

Claims 47-50 and 73-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific mutant CTLA4 molecules such as the L104EA29YIg molecule disclosed in the specification as filed or claimed (e.g. see Example 8 on pages 67-83 of the instant specification),

does not reasonably provide enablement for any “CTLA4 mutant molecule” to be employed as an immunosuppressive agent in the instant claimed methods.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's assertions, filed 10/21/2008, concerning the priority of the instant claims have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant's arguments, filed 10/21/2008, and the examiner's rebuttal concerning the breadth of “soluble CTLA4 mutant molecules” of the instant claims are essentially the same of record and reiterated herein for applicant's convenience.

However, it is noted that the claims now include claims 47-50 and 73-74, given that it does not appear that these claims recite specific mutant CTLA4 molecules.

While applicant relies upon screening CTLA4 mutants for their binding capacity (example 9 on page 71-83 of the instant specification” and the provision of about thirty (30) mutant molecules (e.g., see Table I and II and pages 82-83 and page 70 of the instant specification);

it is noted that the approximately thirty (30) mutant species were chosen from approximately 2300 mutant proteins (e.g., see page 75, lines 28-31 of the instant specification), indicating a number of mutants that apparently did not provide for the functions associated with the claimed methods.

Applicant's arguments have not been found persuasive.

The following is reiterated for applicant's convenience.

Applicant's continual reliance upon amending the claims to recite “soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86” and examples of certain CTLA4 mutant molecules is acknowledged.

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However, the claims relies upon a generic recitation of “a soluble CTLA4 mutant” together with a function but in the absence of a those structures or elements of CTLA4 mutant that are important or critical to a “soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86.

For example, it appears that applicant relies upon the disclosure of U.S. Patent No. 5,773,253; yet the patented claims are still limited in structure as well as function.

Again as pointed out previously, applicant has acknowledged that CTLA4 mutant molecule means wildtype CTLA4 as shown in Figure 19 or any portion or derivative thereof, that has a mutation or multiple mutations and submits Examples of six CTLA4 mutant molecules are provided.

Also, applicant has relied upon disclosing a number of different assays for the identification of CTLA4 mutant molecules as claimed.

However, such assays without more precise guidelines amount to little more than a starting point, a direction for further research. The specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention for any mutant CTLA4 molecule including any mutation or mutations as well as any derivative of CTLA4 as broadly encompassed by the claimed invention. At most, its description will enable a person of skill in the art to attempt to discover how to practice the claimed invention, which is not enough.

Also, the following previously of record is provided for applicant's convenience.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies any “CTLA4 mutant molecule” that inhibits graft rejection encompassed by the claimed methods. “CTLA4 mutant molecule” may have some notion of the source of the “first ligand that interferes with binding of CD28 to either CD80 or CD86”, however, claiming biochemical molecules by a particular name and a modification of said molecule (e.g. “CTLA4 mutant molecule”) by applicant fails to distinctly claim what that “CTLA4 mutant molecule” is and what it is made up of or how it differs from native CTLA4. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any “CTLA4 mutant molecule”.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus of “CTLA4 mutant molecules”. The instant invention encompasses any “CTLA4 mutant molecule”, yet the instant specification does not provide sufficient guidance and direction as to the selection of particular sequences essential for the unrecited (claim 47) and recited function (see claim 48), which interferes with binding of CD28 to either CD80 or CD86 in the inhibition of graft rejection.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g., ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In *re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead to "CTLA4 mutant molecules" other than the CTLA4 mutant molecules disclosed in the specification as filed with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of ligand and receptors encompassed by the claimed invention.

Attwood (Science 290: 471-473, 2000) notes in the Introductory paragraphs that it is presumptuous to make functional assignments merely on the basis of some degrees of similarity between sequences (and it is not always clear what we mean by "function"); very few structures are known compared with the number of sequences, and structure prediction methods are unreliable (and knowing structure does not inherently tell us functions").

Skolnick et al. (Trends in Biotechnology 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

This requirement is emphasized in the instant example since, as summarized in Figures 2 and 3 of Coyle et al. (Nature Immunology 2: 203-209, 2001) the B7-like family members have distinct expression patterns and distinct functions.

Metzler et al. (Nature Structural Biology 4: 527- 531, 1997) describe various CTLA4 mutants and their varying effects on CD80 and CD86 binding (see entire document, including Table 2 on page 530). Here, there does not appear sufficient predictability as to those mutations that result in a particular function, as the mutations had multiple effects on said CD80 and CD86 binding, including little or no effects.

Thus, the experimentation left to those skilled in the art to determine the function of the scope of "CTLA4 mutant molecules" that interfere with binding of CD28 to either CD80 and CD86 and inhibit graft rejection encompassed by the claimed invention is unnecessarily and improperly extensive and undue.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus of "CTLA4 mutant molecules". It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and pharmacology of receptors and ligands.

In the absence of sufficient guidance and direction to the structural and functional analysis, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use "CTLA4 mutant molecules" other than those specific "CTLA mutant molecules" which interfere with the binding of CD28 to either CD80 or CD86 as disclosed in the specification as filed (or as recited in claims 49-50) as the first ligand in the claimed methods to inhibit graft rejection.

Again, applicant is invited to limit the claims to those "CTLA4 mutant molecules" with the appropriate inhibitory properties disclosed in the specification as filed as the first ligand in the claimed methods.

6. **Written Description Rejection.**

This is a written description / not a new matter rejection.

Claims 47-50 and 73-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's assertions, filed 10/21/2008, concerning the priority of the instant claims have been fully considered but have not been found convincing essentially for the reasons of record.

The examiner's rebuttal concerning the breadth of "soluble CTLA4 mutant molecules" of the instant claims is essentially the same rejection of record and reiterated herein for applicant's convenience.

In contrast to relying upon generating, identifying and screening for members of the genus and In particular, upon relying upon screening CTLA4 mutants for their binding capacity (example 9 on page 71-83 of the instant specification" and the provision of about thirty (30) mutant molecules (e.g., see Table I and II and pages 82-83 and page 70 of the instant specification); it is noted that the approximately thirty (30) mutant species were chosen from approximately 2300 mutant proteins (e.g., see page 75, lines 28-31 of the instant specification), indicating a number of mutants that apparently did not provide for the functions associated with the claimed methods.

As addressed previously and reiterated herein, the Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004).

The problem here is that the instant specification fails to provide a disclosure of which residues are required for the "soluble CTLA4 mutant molecule" "to interfere with the binding of CD28 to CD80 and/or CD86", broadly encompassed by the claimed invention.

A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that exhibit this functional property.

Therefore, there is insufficient written description for genera of "soluble CTLA4 mutant molecule" "to interfere with the binding of CD28 to CD80 and/or CD86", broadly encompassed by the claimed invention at the time the invention was made and as disclosed in the specification as filed under the written description provision of 35 USC 112, first paragraph.

However, it is noted that the claims now include claims 47-50 and 73-74, given that it does not appear that these claims recite specific mutant CTLA4 molecules.

Applicant's arguments have not been found persuasive.

The following is reiterated for applicant's convenience.

The instant claims recite and encompass "a soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86" in the absence of those structures or elements of CTLA4 mutant that are important or critical to a "soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86.

As noted in the enablement rejection of record, it appears that applicant relies upon the disclosure of U.S. Patent No. 5,773,253; yet the patented claims are still limited in structure as well as function.

As noted in the enablement rejection of record, applicant has acknowledged that CTLA4 mutant molecule means wildtype CTLA4 as shown in Figure 19 or any portion or derivative thereof, that has a mutation or multiple mutations and submits Examples of six CTLA4 mutant molecules are provided.

Also, applicant has relied upon disclosing a number of different assays for the identification of CTLA4 mutant molecules as claimed.

The recitation of "a soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86" does not meet the written description provision of 35 USC 112, first paragraph.

There is insufficient guidance and direction as to the written description of the claimed "soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86".

Because of the lack of sufficient guidance in determining which structures would lead to "CTLA4 mutant molecules" other than the CTLA4 mutant molecules disclosed in the specification as filed with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.);

one of skill in the art would conclude that applicant was not in possession of the structural attributes of a representative number of species possessed by the members of the genera of "soluble CTLA4 mutant molecules", broadly encompassed by the claimed invention.

Attwood (Science 290: 471-473, 2000) notes in the Introductory paragraphs that it is presumptuous to make functional assignments merely on the basis of some degrees of similarity between sequences (and it is not always clear what we mean by "function"); very few structures are known compared with the number of sequences, and structure prediction methods are unreliable (and knowing structure does not inherently tell us functions").

Skolnick et al. (Trends in Biotechnology 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

This requirement is emphasized in the instant example since, as summarized in Figures 2 and 3 of Coyle et al. (Nature Immunology 2: 203-209, 2001) the B7-like family members have distinct expression patterns and distinct functions.

Metzler et al. (Nature Structural Biology 4: 527- 531, 1997) describe various CTLA4 mutants and their varying effects on CD80 and CD86 binding (see entire document, including Table 2 on page 530). Here, there does not appear sufficient predictability as to those mutations that result in a particular function, as the mutations had multiple effects on said CD80 and CD86 binding, including little or no effects.

The instant application has not provided a sufficient description showing possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genera of "soluble CTLA4 mutant molecules", broadly encompassed by the claimed invention.

Further, the Court has interpreted 35 U.S.C. §112, first paragraph, to require the patent specification to "describe the claimed invention so that one skilled in the art can recognize what is claimed." Enzo Biochem, Inc. v. Gen-Probe Inc., 63 USPQ2d 1609 and 1618 (Fed. Cir. 2002). In evaluating whether a patentee has fulfilled this requirement, our standard is that the patent's "disclosure must allow one skilled in the art 'to visualize or recognize the identity of' the subject matter purportedly described." Id. (quoting Regents of Univ. of Cal. v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed Cir. 1997)).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483.

The Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004).

The problem here is that the instant specification fails to provide a disclosure of which residues are required for the "soluble CTLA4 mutant molecule" "to interfere with the binding of CD28 to CD80 and/or CD86", broadly encompassed by the claimed invention.

A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that exhibit this functional property.

Therefore, there is insufficient written description for genera of "soluble CTLA4 mutant molecule" "to interfere with the binding of CD28 to CD80 and/or CD86", broadly encompassed by the claimed invention at the time the invention was made and as disclosed in the specification as filed under the written description provision of 35 USC 112, first paragraph.

Applicant has been reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

7. Claims 1-6, 9-13, 17, 30, 33-37, 44-52, 54-64 and newly submitted claims 75-77 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Sykes (U.S. Patent No. 6,514,513) in view of art known practice and modes of administration of alkylating agents

such as busulfan / cyclophosphamide at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4), Slattery et al. Therapeutic Drug Monitoring 20: 543-549, 1998) and Hassan et al. (Blood 84: 2144-2150, 1994) , The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 (see pages 1067-1074; particularly page 1072; Immunosuppression, Cyclophosphamide) and Shichi et al. (U.S. Patent No. 4,843,092), Strom et al. (in Therapeutic Immunology edited by Austen et al., Blackwell Science, Cambridge, MA, 1996; see pages 451-456), Sykes et al. (Nature Medicine 3: 783-787, 1997) and Wekerle et al. (J. Exp. Med. 187: 2037-2044, 1998)

and in further view of

Reinherz et al. (U.S. Patent No. 4,443,427), Tomita et al. (J. Immunol. 164: 34-41, 2000) (1449; Exhibit #274), Bingaman et al. (Transplantation 69: 2491-2496, 2000) (1449; Exhibit 193), Larsen et al. (Current Opinion in Immunology 9: 641-647) (1449; Exhibit 188), and Schaub et al. (Journal of Allergy and Clinical Immunology 99: 5206, Abstract 843, 1997) (1449; #264) essentially for the reasons of record.

Applicant's arguments, in conjunction with certain legal decisions and Exhibits, filed 10/21/2008, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant's arguments, filed 10/21/2008, and the examiner's rebuttal concerning the obviousness of the claimed methods are essentially the same of record and reiterated herein for applicant's convenience.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather merely asserts that these prior art references fail to teach and, do not provide sufficient suggestion or motivation to use busulfan in the claimed methods for facilitating mixed hemopoietic chimerism and tolerance induction and does not address the teachings of the references individually and not their teachings individually or in combination.

One cannot show non-obviousness by merely asserting that the references do not provide the sufficient elements of obviousness or by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

The prior art recognized the combination of immunosuppressive therapies addressing different targets to increase the desired immunosuppressive effect and to decrease the toxicity of each immunosuppressive in such regimens rather than an explicit teaching of using busulfan in the claimed methods for facilitating mixed hemopoietic chimerism and tolerance induction.

With respect to applicant's arguments addressing each reference of record separately, the teachings and the rebuttals of applicant's arguments with respect to each reference have been addressed previously and are reiterated below.

With respect to applicant's reliance upon the newly submitted Exhibits to support that the claimed invention possesses unexpected advantages that the cited references do not teach, the following is noted.

Applicant's reliance upon the apparent assertions based upon certain observations in the experimental models in the Exhibits (see rebuttal herein) are not necessarily commensurate in scope with the claimed invention, including the reliance of certain observations in these experimental models on the scope of the claimed methods.

Giving the claims the broadest reasonable interpretation, see *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (during ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification), the claims read on methods of inhibiting the rejection of transplants with T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and anti-CD40 antibody antagonists, wherein there is a resultant inhibition of rejection of the solid organ or tissue/cellular transplant.

The claims do not specify any level of inhibition of transplant rejection, thus the claims read on any measurable inhibition of transplant rejection.

Also, note that the administration of depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and/or anti-CD40 antibody antagonists were useful in the promotion of transplant survival, wherein there would also be a resultant inhibition of rejection of the transplant.

For example in the context of depleted bone marrow cells and busulfan, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant.

See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings."); *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); *In*

re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991) (discussed below). Although Ex parte Levengood, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) states that obviousness cannot be established by combining references "without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done" (emphasis added), reading the quotation in context it is clear that while there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention.

With respect to Exhibit B: Kean et al., Blood 99: 1840-1849, 2002;
the claims are not limited to a cure for murine sickle cell disease in a murine experimental model.

Also, as Kean et al. discuss the limitation of their observations in this experimental system, "Perhaps most importantly, how will these results be transplanted to affect human SCD patients? Clearly, this is just the first step in the long road toward developing nonmyeloablative transplantation and tolerance induction for SCD patients"

See entire document, including the Discussion, particularly page 1848, last paragraph.

With respect to Exhibit C: Guo et al., American Journal of Transplantation 3: 1091-1098, 2003;

the claims are not limited to long-term survival of intestinal allografts induced by costimulation blockade, busulfan and donor bone marrow infusion,

Guo et al. noted that

"Although this is the most effective protocol that we have tested using this stringent model of transplantation, our observations suggest that modifications will be necessary before it can be reliably application to the transplantation of highly immunogenic organs like the intestine."

See entire document, including Abstract, particularly the last line and page 1092, column 1, paragraph 1.

Also, note that this reference acknowledges the effectiveness of costimulation blockade, busulfan and donor bone marrow infusion in promoting graft survival in transplantation systems other than intestinal transplants (e.g., see Introduction and Discussion).

With respect to Exhibit D: Shirasugi et al., The Journal of Immunology 169: 2677-2684, 2002;

the claims are not limited to murine cardiac allografts.

For example, Tufveson et al. (Immunological Reviews 1365: 99-109, 1993) note that:

"A main problem in the rodent model for organ allografting is the ease with which rejection is usually suppressed."

See entire document, including page 100, Testing New Drugs in Animal Models.

Also, note that Shirsagui et al. acknowledge

That tolerance induction regimens have incorporated the use of inhibitors of CD28/B7 and CD40/CD154 pathways (see page 2677, column 2, paragraph 1 and Discussion) and

that the induction of mixed hemopoietic chimerism has been a promising strategy for the induction of robust immunological tolerance for many years (e.g., see page 2677, column 2, paragraph 2 and Discussion).

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International Co. v. Teleflex Inc. 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted as well:

A) Combining prior art elements according to known methods to yield predictable results.

The rationale to support a conclusion that the claims would have been obvious is that all the claimed elements (e.g. T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and CD40:CD40L antagonists in the use of inhibiting rejection of a solid organ, tissue or cellular transplant) were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods (administering said antagonists in transplantation regimens, including the induction of long term survival of transplants of interest with no change in their respective functions and the combination would have yielded nothing more than predictable results of inhibiting the rejection of transplants with T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and anti-CD40 antibody antagonists.

B) Use of known technique to improve similar products in the same way.

The rationale to support a conclusion that the claims would have been obvious is that a method of inhibiting rejection of a transplant or of promoting transplant survival via the administration of T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and CD40:CD40L antagonists decreasing the immunogenicity was made part of ordinary capabilities of one skilled in the art based upon the teachings of the prior art. One of ordinary skill in the art would have been capable of applying the known T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and CD40:CD40L antagonists to inhibit graft rejection and to promote transplant survival would have been predictable to one of ordinary skill in the art.

C) Applying a known technique to a known product ready for improvement to yield predictable results.

The rationale to support a conclusion that the claims would have been obvious is that a particular known technique (administering T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and CD40:CD40L antagonists to inhibit graft rejection and/or to promote transplant survival) was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique of combining known products to inhibit graft rejection and/or to promote graft survival (e.g. T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and CD40:CD40L antagonists) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

D) "Obvious to try" --- choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options (e.g. combining the administration of T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and CD40:CD40L antagonists to inhibit graft rejection and/or to promote graft survival) within his or her technical grasp. This leads to the anticipated success of inhibiting graft rejection and/or of promoting transplant survival with the combination of T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and CD40:CD40L antagonists. It is likely the product not of innovation but of ordinary skill and common sense.

E) Some teachings, suggestion, or motivation in the prior art that would have lead one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

Since of inhibiting graft rejection and/or of promoting transplant survival with the combination of T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and CD40:CD40L antagonists would have been predictable at the time of the invention, there would have been reasonable expectation of successful development of transplantation regimens as claimed. The prior art had recognized the obstacles of inhibiting graft rejection and/or of promoting transplant survival and had suggested and relied upon the administration of T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and CD40:CD40L antagonists agonistic / activating anti-CD40 antibodies, including combinations thereof to accomplish this goal. The claims were obvious because it would have been obvious to try the known T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and CD40:CD40L antagonists agonistic / activating anti-CD40 antibodies, including combinations thereof to inhibit graft rejection and/or to promote transplant survival in the absence of administering tumor antigen with a reasonable expectation of success.

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"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosset*, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to inhibit graft rejection and to promote graft survival in transplantation regimens, incorporating the known administration of T cell depleted bone marrow cells, alkylating agents such as busulfan, CTLA4 antagonists and CD40:CD40L antagonists agonistic / activating anti-CD40 antibodies, including combinations thereof, to accomplish this goal would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing therapeutic regimens to improve graft survival.

Applicant's arguments have not been found persuasive.

Applicant's arguments have not been found persuasive.

The following is reiterated for applicant's convenience.

Given the broadest reasonable interpretation of the claimed methods that administering an alkylating agent subsequently after administering T cell depleted bone marrow, the following is noted.

Reinherz et al.

Reinherz et al. teach the use of busulfan and immunosuppressives such as cytoxan (i.e., cyclophosphamide) when reconstitution failed (e.g., see column 7, paragraph 3).

Therefore, Reinherz et al. teach the use of busulfan and cyclophosphamide in a conditioning regimen subsequent to previous attempts to transplant bone marrow and in turn, support the obviousness of record in the use of busulfan and cyclophosphamide subsequent to bone marrow transplantation in circumstances wherein additional bone marrow transplantation occurs or is desirable.

Given the broadest reasonable interpretation of the claimed methods that administering an alkylating agent subsequently after administering T cell depleted bone marrow,

Reinherz et al. provides additional evidence to the record, particularly the multiple infusions taught by Sykes et al., that the claimed methods encompass providing busulfan and/or cyclophosphamide subsequently to T cell depleted bone marrow, subsequent to previous attempts to transplant bone marrow.

The claimed methods do not recite a specific temporal element that excludes multiple infusions or attempts to transplant bone marrow and multiple conditioning regimens, including the use of busulfan and/or cyclophosphamide.

Tomita et al.

In addition, given the broadest reasonable interpretation of the claimed methods that administering an alkylating agent subsequently after administering T cell depleted bone marrow,

Tomita et al. provides for administering busulfan and cyclophosphamide the same day as spleen cells, which provides for the obviousness of providing said alkylating agents subsequent to administering bone marrow, given the use of alkylating agents after administering hemopoietic cells had advantages when given at the same or nearly the same time.

The claimed methods do not recite a specific temporal time frame other than “after”. Therefore, when alkylating agents and hemopoietic cells are given the same day, it would have been obvious that one could be given prior to the other or vice versa and not necessarily at exactly the same time or in the same infusion.

Tomita et al. teach regimens incorporating cyclophosphamide and busulfan along with T cell-depleted bone marrow cells for the induction of mixed chimerism and skin allograft tolerance (see entire document, including Abstract, Results and Discussion)

Also, note that more consistent stable mixed chimerism was achieved by the addition of busulfan on day three (day 3) to the spleen cells and cyclophosphamide Groups (e.g., Groups 10 and 11). Wherein it is noted that days two and three (days 2 and 3) are the days of the administration of T cell depleted bone marrow (see Results, particularly page 36, column 2 in Induction of long-lasting mixed chimeric and skin allograft prolongation by the additional myelosuppressive treatments).

In contrast to applicant's assertions of unexpected advantages, the following is noted.

Bingaman et al. teach methods of transplantation of bone marrow in the form of a bone graft to facilitate hemopoietic chimerism and long-term donor-specific hyporesponsiveness (e.g., skin grafts) in the absence of cytoreductive conditioning regimen by employing combined blockade of the CD40 and CD28 costimulatory pathways (See entire document, including Abstract and Discussion).

Larsen et al. teach the advantages and extreme potent inhibition of the simultaneous blockade of the CD40-CD40 and B7-CD28 pathways to inhibit allograft rejection and its applicability to transplantation tolerance clinically (see entire document, including Strategies to induce graft acceptance or tolerance by manipulating CD40 and Conclusions on pages 644-645).

Schaub et al. teach the synergistic effect of blocking, including sequential blockade, of the CD28/B7 and CD40L/CD40 costimulatory pathways in the treatment of autoimmune responses (see Abstract).

Therefore, in contrast to applicant's assertions of unexpected advantages, the additional references of Bingaman et al. and Tomita et al. teach the advantages of mixed chimerism in combination therapy to induce long-term antigen-specific unresponsiveness and

the additional references of Bingaman et al., Larsen et al. and Schaub et al. teach the advantages, including synergistic effects, of combining blocking both the CD28/B7 and CD40L/CD40 costimulatory pathways in achieving long-term antigen-specific unresponsiveness.

With respect to applicant's assertions filed 12/28/2007 in the Appeal Brief concerning the obviousness of the instant claims have been fully considered but have not been found convincing essentially for the reasons of record.

In addition to the newly added references above, applicant's arguments and the examiner's rebuttal concerning the obviousness of the instant claims are essentially the same of record and reiterated herein for applicant's convenience.

Applicant's arguments have not been found persuasive.

Also, as indicated previously, the following of record is reiterated for applicant's convenience.

As indicated previously, with respect to applicant's assertions concerning the newly added Strom et al. (in *Therapeutic Immunology* edited by Austen et al., Blackwell Science, Cambridge, MA, 1996; see pages 451-456), Sykes et al. (*Nature Medicine* 3: 783-787, 1997) and Wekerle et al. (*J. Exp. Med.* 187: 2037-2044, 1998) to the previous rejection of record, the following is noted.

With respect to Strom et al., Sykes et al. and Wekerle et al., applicant asserts that these references fail to teach the use of busulfan in the claimed methods for facilitating mixed hemopoietic chimerism and tolerance induction.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. *In re Keller*, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather merely asserts that these prior art references fail to teach and, do not provide sufficient suggestion or motivation to use busulfan in the claimed methods for facilitating mixed hemopoietic chimerism and tolerance induction and does not address the teachings of the references individually and not their teachings individually or in combination.

One cannot show non-obviousness by merely asserting that the references do not provide the sufficient elements of obviousness or by attacking references individually where the rejections are based on a combination of references. *In re Young* 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

These previously newly added references were provided to make it clear that the prior art recognized the combination of immunosuppressive therapies addressing different targets to increase the desired immunosuppressive effect and to decrease the toxicity of each immunosuppressive in such regimens rather than an explicit teaching of using busulfan in the claimed methods for facilitating mixed hemopoietic chimerism and tolerance induction.

Strom et al. teach that it was known and practiced by the ordinary artisan to employ a multitiered approach to immunosuppressive therapy similar in principle to that used in chemotherapy, several agents are used simultaneously, each of which is directed to a different molecular target with the allograft response. Additive-synergistic effects are achieved through application of each agent at relatively low dose, thereby limiting the toxicity of each individual agent while increasing the total immunosuppressive effect (see entire document, including the introduction on page 451).

Sykes et al. also teach the advantages of mixed chimerism in employing immunosuppressive regimens associated with hemopoietic cell transplantation in the induction of central T cell tolerance for clinical use (see entire document, including Abstract and the last paragraph on page 786).

Wekerle et al. also teach the advantages of employing inhibitors of costimulation and CD40:CD40 ligand interactions that lead to chimerism in approaches to induce tolerance and overcome the problems of chronic organ graft rejection and immunosuppression-related toxicity (See entire document, including Abstract, Introduction and Discussion).

Again, in contrast to applicant's assertions of insufficient teachings in the prior art or unexpected advantages, the prior art provides for the combination therapy encompassed by the claimed methods for the same or nearly the same reasons, that is, to achieve long term graft survival and reducing immunosuppression-related toxicities by combining inhibitors of B7:CD28:CTLA4 and CD40:CD40L pathways with standard or current immunosuppression regimens at the time the invention was made with an expectation of success in achieving said goals.

Applicant's continual assertions in the absence of objective evidence to the contrary that the teaching of Sykes that busulfan may be used in lieu of irradiation to create hemopoietic space runs contrary to the clear teaching of the prior art or what was known and practiced for decades by the ordinary artisan.

Also, as previously noted, Hassan et al. clearly states:

"Busulfan has been introduced as an alternative for total body irradiation (TBI). The therapeutic efficacy for busulfan / cyclophosphamide is considered to be equivalent if not superior to cyclophosphamide and TBI."

See page 2144, column 1 of Hassan et al. (Blood 84: 2144-2150, 1994).

Also, as indicated by the various citations of record, busulfan was commonly used in combination with other immunosuppressive regimens in therapeutic regimens of hemopoietic / bone marrow transplantation by the ordinary artisan at the time the invention was made. See the prior art of record, including the background or introductory information provided by Hassan et al. Slattery et al. as well as Sykes et al. and the Andersson et al. U.S. Patent Nos. 5,430,057 and 5,559,148.

Therefore, applicant's continual assertions that busulfan or other alkylating agents were not employed in transplantation at the time the invention was made simply runs contrary to the clear teachings of the prior art references.

In contrast to applicant's continual assertions, the prior art did not limit the use of busulfan to cancer patients alone.

The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C).

One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

For example, in contrast to applicant's continual assertions that Andersson et al. U.S. Patent Nos. 5,430,057 and 5,559,148 are directed to the treatment of neoplasms and fail to teach the use of busulfan together with other agents for facilitating hemopoietic chimerism,

Applicant still appears to ignore their own acknowledgement on pages 26-27 of the instant specification, which includes the citation of Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148; see entire documents) that methods of administering busulfan in therapeutic regimens were known and practiced at the time the invention was made.

Further, it has been noted that the Background of the Invention of Andersson et al.'s Patents clearly describe the well known use of busulfan in hemopoietic autologous and allogeneic transplantation as well as its advantages at the time the invention was made (also, see Summary of the Invention and Detailed Description of the Preferred Embodiments).

Also, in contrast to applicant's continual assertions concerning effective dosages, the specification as-filed (e.g. see page 27, paragraph 2) is consistent with the prior art in that "the amount of alkylating agent and T cell depleted bone marrow may be determined by routine experimentation and optimized empirically" and discloses dosages consistent with the prior art.

Applicant's arguments are not consistent with the disclosure of the instant application as filed as well as with the teachings of the prior art, including references relied or disclosed in the application as-filed.

Therefore, one of ordinary skill in the art would have been motivated to administer busulfan at various times, including the claimed timing (e.g. see claims 30-32) to create hemopoietic space for T cell depleted bone marrow / stem cells as well as to optimize bioavailability.

Applicant's continual reliance upon the unexpected advantages of combining busulfan with costimulation blockade by relying upon the Exhibits of Kean et al., Guo et al. and Sirasugi et al. have not been found convincing in light of the clear teachings of the prior art in combining the claimed elements of bone marrow cells, hemopoietic space agents, including busulfan as well as CD40L:CD40 and CD28:B7 antagonists in tissue and organ transplantation.

Again as pointed out previously repeatedly, Sykes teach methods inducing specific nonresponsiveness or tolerance to various antigens by inducing hemopoietic chimerism, including transplant antigens by administering T cell depleted bone marrow cells / stem cells (e.g. see columns 6-7; column 8, lines 53-55; columns 9-11, column 15, paragraph 1) (note: stem cells read on T cell depleted bone marrow cells); hemopoietic space agents, including busulfan (e.g. see column 8, paragraph 1); CD40L-CD40 inhibitors, including antibodies that bind CD40 and CD28-B7 inhibitors, including CTLA4Ig (e.g. see column 8, line 65 - column, line 36; column 12) as it relates to tissue and organ transplantation (see entire document, including Summary of the Invention; Detailed Description; Claims).

In addition, Sykes describes numerous modes of administration of providing the above-mentioned elements of therapeutic regimen in combination before, concurrently and subsequent to transplantation (see Summary of the Invention and Detailed Description).

Administering bone marrow stem cells, including repeated administration of said cells prior to, during and after the transplant are described (see Summary of the Invention, including column 2, line 60 – column 3, line 49; and Detailed Description, including column 6, line 38 – column 7, line 46; columns 9 – 10)

While Sykes differs from the claimed methods by not disclosing the particular timing of busulfan in the claimed therapeutic methods to promote graft survival (e.g. see claims 30-32), applicant's continual assertions that the prior art teachings does not provide for the various elements employed in promoting long term transplant survival ignores the clear teachings of the prior art.

In this case, the teachings of the prior art pertaining to the difficulties in achieving long term transplant survival and in the success in combining different immunosuppressive regimens to solve similar problems as applicant's invention would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144

the following previously newly added references were provided to make it clear that the prior art recognized the combination of immunosuppressive therapies addressing different targets to increase the desired immunosuppressive effect and to decrease the toxicity of each immunosuppressive in such regimens.

Strom et al. teach that it was known and practiced by the ordinary artisan to employ a multitiered approach to immunosuppressive therapy similar in principle to that used in chemotherapy, several agents are used simultaneously, each of which is directed to a different molecular target with the allograft response. Additive-synergistic effects are achieved through application of each agent at relatively low dose, thereby limiting the toxicity of each individual agent while increasing the total immunosuppressive effect (see entire document, including the introduction on page 451).

Sykes et al. also teach the advantages of mixed chimerism in employing immunosuppressive regimens associated with hemopoietic cell transplantation in the induction of central T cell tolerance for clinical use (see entire document, including Abstract and the last paragraph on page 786).

Wekerle et al. also teach the advantages of employing inhibitors of costimulation and CD40:CD40 ligand interactions that lead to chimerism in approaches to induce tolerance and overcome the problems of chronic organ graft rejection and immunosuppression-related toxicity (See entire document, including Abstract, Introduction and Discussion).

In contrast to applicant's continual assertions of insufficient teachings in the prior art or unexpected advantages, the prior art provides for the combination therapy encompassed by the claimed methods for the same or nearly the same reasons, that is, to achieve long term graft survival and reducing immunosuppression-related toxicities by combining inhibitors of B7:CD28/CTLA4 and CD40:CD40L pathways with standard or current immunosuppression regimens at the time the invention was made with an expectation of success in achieving said goals.

Again, the following of record is provided for applicant's convenience addresses applicant's arguments of record and those reiterated in applicant's amendment, filed 12/18/06.

While applicant continually argues that Sykes does not expressly disclose that administering busulfan in amounts that facilitates mixed hemopoietic chimerism, one cannot separate a product from its properties. Further, in this case, applicant acknowledges the use of busulfan to create hemopoietic space, therefore the effective amount of busulfan taught by the prior art does inherently facilitate hemopoietic chimerism.

With respect to the use an alkylating agent such as cyclophosphamide as an immunosuppressive agent, which can be administered subsequent to the administering T cell depleted bone marrow cells to a subject in a transplantation regimen, the following is noted.

The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 describes the known use of immunosuppressive drugs such as the alkylating agent cyclophosphamide in after transplantation and during rejection crises as well as maintenance regimens with relatively small doses of immunosuppressants (see pages 1067-1074; particularly page 1072; Immunosuppression, Cyclophosphamide).

Shichi et al. (U.S. Patent No. 4,843,092) similarly teach the known use of immunosuppressive agents such as the alkylating agent cyclophosphamide as agents for suppressing rejection which may occur after transplantation of human organs (see column 1, second paragraph of Background Art).

Therefore, one of ordinary skill in the art would have administered the alkylating agent cyclophosphamide at various times prior to, during and subsequent to transplanting cells and tissues in order to provide the appropriate immunosuppressive environment to promote long term acceptance of transplants / grafts. It is clear that cyclophosphamide has been used for decades by the ordinary artisan in transplantation regimens.

Also, as indicated previously, the claimed timing and dosages of alkylating agents including busulfan or cyclophosphamide in the claimed therapeutic methods to inhibit rejection of transplant was obvious to one of ordinary skill in the art at the time the invention was made, as these limitations appear to be consistent with those employed in the prior art and with providing efficacy and bioavailability, while minimizing drug associated toxicities.

The following of record is provided for applicant's convenience addresses applicant's arguments of record and those reiterated in applicant's amendment, filed 3/27/06.

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Sykes teach methods inducing specific nonresponsiveness or tolerance to various antigens by inducing hemopoietic chimerism, including transplant antigens by administering

T cell depleted bone marrow cells / stem cells (e.g. see columns 6-7; column 8, lines 53-55; columns 9-11, column 15, paragraph 1) (note: stem cells read on T cell depleted bone marrow cells);

hemopoietic space agents, including busulfan (e.g. see column 8, paragraph 1);,

CD40L-CD40 inhibitors, including antibodies that bind CD40 and

CD28-B7 inhibitors, including CTLA4Ig (e.g. see column 8, line 65 - column, line 36; column 12)

as it relates to tissue and organ transplantation (see entire document, including Summary of the Invention; Detailed Description; Claims).

In addition, Sykes describes numerous modes of administration of providing the above-mentioned elements of therapeutic regimen in combination before, concurrently and subsequent to transplantation (see Summary of the Invention and Detailed Description).

Administering bone marrow stem cells, including repeated administration of said cells prior to, during and after the transplant are described (see Summary of the Invention, including column 2, line 60 - column 3, line 49; and Detailed Description, including column 6, line 38 - column 7, line 46; columns 9 - 10)

Sykes differs from the claimed methods by not disclosing the particular timing of busulfan in the claimed therapeutic methods to promote graft survival (e.g. see claims 30-32). Claims 1-2 and 9-10 encompass the particular timing of busulfan administration encompassed by claims 30-32.

As acknowledged on pages 26-27 of the instant specification including the citation of Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148; see entire documents); modes of administering busulfan were known at the time the invention was made. Therefore, one of ordinary skill in the art would have been motivated to administer busulfan at various times, including the claimed timing (e.g. see claims 30-32) to create hemopoietic space for T cell depleted bone marrow / stem cells as well as to optimize bioavailability.

Slattery et al. teach that busulfan is an alkylating agents commonly used to ablate marrow before hemopoietic stem cell transplantation and the importance of analytical and pharmacokinetic aspects of therapeutic monitoring (see entire document, including the Summary on page 543). It is noted that the patients received busulfan doses every 6 hours over a period of 4 days (see Busulfan Concentration and Outcome of Transplantation).

Similarly Hassan et al. teach the known use of busulfan in myeloablative therapy in bone marrow transplantation and the importance of drug monitoring and individual dose adjustment in providing for busulfan bioavailability while reducing / avoiding drug-related toxicities (See entire document, including the Abstract).

Therefore, the claimed timing of busulfan in the claimed therapeutic methods to inhibit rejection of transplant was obvious to one of ordinary skill in the art at the time the invention was made, as these limitations appear to be consistent with those employed in the prior art and with providing busulfan efficacy and bioavailability, while minimizing drug associated toxicities.

Given the general applicability and desirability of the modes of inducing immunological nonresponsiveness to a variety of antigens, including a wide variety of cells, tissues and organs of interest, one of ordinary skill in the art would have been motivated to include the well known transplantation of skin grafts to the transplantation regimens taught by Sykes.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive

8. Claims 1, 9 and 33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Sykes (U.S. Patent No. 6,514,513)

in view of art known practice and modes of administration of alkylating agents such as bulsulfan / cyclophosphamide at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4), Slattery et al. Therapeutic Drug Monitoring 20: 543-549, 1998) and Hassan et al. (Blood 84: 2144-2150, 1994), The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 (see pages 1067-1074; particularly page 1072; Immunosuppression, Cyclophosphamide) and Shichi et al. (U.S. Patent No. 4,843,092), Strom et al. (in Therapeutic Immunology edited by Austen et al., Blackwell Science, Cambridge, MA, 1996; see pages 451-456), Sykes et al. (Nature Medicine 3: 783-787, 1997) and Wekerle et al. (J. Exp. Med. 187: 2037-2044, 1998)

and further in view of

Reinherz et al. (U.S. Patent No. 4,443,427), Tomita et al. (J. Immunol. 164: 34-41, 2000) (1449; Exhibit #274), Bingaman et al., Transplantation 69: 2491-2496 (2000) (1449; Exhibit 193), Larsen et al., Current Opinion in Immunology 9: 641-647 (1449; Exhibit 188), and Schaub et al., Journal of Allergy and Clinical Immunology 99: 5206, Abstract 843 (1997) (1449; #264) and in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449, Exhibit 225) essentially for the reasons of record.

Applicant's arguments, in conjunction with certain legal decisions and Exhibits, filed 10/21/2008, have been fully considered but have not been found convincing essentially for the reasons of record and that addressed above in Section 7.

Applicant's arguments, filed 10/21/2008, and the examiner's rebuttal concerning the obviousness of the claimed methods are essentially the same of record and that addressed above in Section 7 and reiterated herein for applicant's convenience.

Applicant's arguments have not been found persuasive.

The following is reiterated for applicant's convenience.

The teachings are set forth above.

As indicated previously, Sykes differs from the claimed methods by not disclosing "skin" per se as the tissue of organ of interest for transplantation. Claims 1 and 9 encompass skin grafts as the tissue / organ transplant of the claimed methods

Larsen et al. teach modes of inhibiting immune responses, including rejection of various tissues and organs including skin (e.g. see column 2; column 6, paragraph 4) by blocking CD40:CD40L and CTLA4:CD28:B7 pathways in order to induce immunological unresponsiveness in the transplant recipient (see entire document, including Background of the Invention, Summary of the Invention, Detailed Description and Claims).

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Given the general applicability and desirability of the modes of inducing immunological nonresponsiveness to a variety of antigens, including a wide variety of cells, tissues and organs of interest, as taught by Sykes and Larsen et al., one of ordinary skill in the art would have been motivated to include the well known transplantation of skin grafts to the transplantation regimens taught by Sykes, given the evidence by Larsen et al. that skin is among a list of known tissues that were routinely transplanted at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

9. Claims 1, 5, 6, 9-10, 12-23, 30, 34, 36-37, 44-52, 54-60, 62-74 and newly added claims 75-77 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Sykes (U.S. Patent No. 6,514,513)

in view of art known practice and modes of administration of alkylating agents such as bulsulfan / cyclophosphamide at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4), Slattery et al. Therapeutic Drug Monitoring 20: 543-549, 1998) and Hassan et al. (Blood 84: 2144-2150, 1994), The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 (see pages 1067-1074; particularly page 1072; Immunosuppression, Cyclophosphamide) and Shichi et al. (U.S. Patent No. 4,843,092), Strom et al. (in Therapeutic Immunology edited by Austen et al., Blackwell Science, Cambridge, MA, 1996; see pages 451-456), Sykes et al. (Nature Medicine 3: 783-787, 1997) and Wekerle et al. (J. Exp. Med. 187: 2037-2044, 1998)

and in further view of Reinherz et al. (U.S. Patent No. 4,443,427), Tomita et al. (J. Immunol. 164: 34-41, 2000) (1449; Exhibit #274), Bingaman et al., Transplantation 69: 2491-2496 (2000) (1449; Exhibit 193), Larsen et al., Current Opinion in Immunology 9: 641-647 (1449; Exhibit 188), and Schaub et al., Journal of Allergy and Clinical Immunology 99: 5206, Abstract 843 (1997) (1449; #264)

and in view of Peach et al. (US 20020182211) essentially for the reasons of record.

Applicant's arguments, in conjunction with certain legal decisions and Exhibits, filed 10/21/2008, have been fully considered but have not been found convincing essentially for the reasons of record and that addressed above in Section 7.

Applicant's arguments, filed 10/21/2008, and the examiner's rebuttal concerning the obviousness of the claimed methods are essentially the same of record and that addressed above in Section 7 and reiterated herein for applicant's convenience.

Applicant's arguments have not been found persuasive.

The teachings are set forth above.

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The following is reiterated for applicant's convenience.

Sykes differs from the claimed methods by not disclosing the particular mutant CTLA4 mutant molecules, including L104EA29YIg CTLA4 recited in the instant claims as the inhibitory CTLA4 of the claimed invention, including the soluble CTLA4 mutants of newly added claims 65-74.

Peach et al. teach soluble CTLA4 mutant molecules, including the specific L104EA29YIg, which have greater avidity than CTLA4 and can bind either of CD80, CD86 or both (e.g., see Summary of the Invention) in immunomodulating regimens for the treatment or prevention of acute or chronic graft rejection, including in combination therapy (e.g. see paragraphs [0079] – [0084] on pages 8-9). The claimed extracellular domains as well as the claimed sequences (e.g. claims 44-52 and 56) are intrinsic properties of the referenced CTLA4 mutant molecules, including the specific L104EA29YIg taught by Peach et al.

Given the greater avidity soluble CTLA4 mutant molecules, including the specific L104EA29YIg, which can bind either of CD80, CD86 or both, one of ordinary skill in the art would have been motivated to substitute said soluble CTLA4 mutant molecules taught by Peach et al. in the referenced transplantation regimens taught by Sykes, in an effort to increase the efficacy of CTLA4 molecules to inhibit the desired CTLA4-mediated responses in promoting long term graft survival at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/
Primary Examiner
Art Unit 1644
Technology Center 1600
January 21, 2009

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